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Case report

Late-onset Pompe disease associated with polyneuropathy

M. Lamartine S.Monteiro, G. Remiche*

Centre de Référence Neuromusculaire, Department of Neurology, Service de Neurologie, Hôpital Erasme, Université Libre de Bruxelles (ULB), Route de Lennik 808, 1070 Brussels, Belgium

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Abstract

Late-onset Pompe disease is caused by a glycogen deposition involving mainly striated muscle. It may also target many other tissues such as liver, smooth muscles or spine anterior horn. Glycogen accumulation in Schwann cells and in the perineurium of peripheral nerves was shown in Pompe's disease mouse models. Moreover two late-onset Pompe disease patients were reported as having a small fiber neuropathy. To the best of our knowledge an involvement of large nerve fibers was never depicted. We describe four late-onset Pompe disease patients having a concomitant polyneuropathy of undetermined etiology. Our observations reinforce the proof-of-concept supporting a potential involvement of peripheral nerves as additional organ targeted by late-onset Pompe disease. It has clinical care consequences since peripheral neuropathy in late-onset Pompe disease could worsen patient's disability and needs particular care such as proprioceptive physiotherapy.

Keywords: Polyneuropathy; Late-onset Pompe disease.

1. Introduction

Late-onset Pompe disease (LOPD) is a rare autosomal recessive disease caused by acid alpha-1,4-glucosidase (GAA) lysosomal enzyme deficiency.

Glycogen deposition in Pompe disease mainly involves striated muscle but may also target many other tissues such as liver, smooth muscle or spinal anterior horn cells.

Glycogen accumulation in Schwann cells and in the perinerium of peripheral nerves was shown in Pompe's disease mouse models [1].

Moreover, some cases of Pompe disease patients were reported as having a small fiber neuropathy [2].

To the best of our knowledge an involvement of large nerve fibers was never depicted.

The aim of this study is to describe LOPD patients having a concomitant polyneuropathy of undetermined etiology and to discuss the potential involvement of peripheral nerves in LOPD.

2. Case report

We retrospectively collected medical records data of the LOPD patients followed in our neuromuscular reference center (Hôpital Erasme, Université Libre de Bruxelles).

Inclusion criteria were: (1) age >18 years; (2) at least two of the following criteria: −1- abnormal low GAA enzyme activity assay measured in at least in one tissue, −2- myopathic changes on muscle biopsy including glycogen deposition evidence and −3- two pathogenic mutations on *GAA* gene [3]; (3) availability of neurological examination and electroneuromyography reports in the medical record.

Ethic committee agreement was obtained before starting this study.

We found that four of the six LOPD patients in our database met the criteria for polyneuropathy diagnosis.

The diagnosis of polyneuropathy was made following the international clinical and electroneuromyographic criteria [4]. The presence of potential etiologies for polyneuropathy was systematically reassessed as showed in Table 1 [5].

Based upon world health organization recommendations, none of our patients disclosed a chronic alcohol abuse.

* Corresponding author.
E-mail address: gauthier.remiche@erasme.ulb.ac.be (G. Remiche).

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Table 1
Screened polyneuropathy etiologies excluded in our LOPD patients.

Autoimmune[1]	**Inherited**[4]
Lupus Erythematosus, Systemic	CMT
Rheumatoid arthritis	HNPP
Sarcoidosis	
Secondary amyloidosis	**Metabolic**[5]
Sjögren syndrome	Diabetes
	Prediabetes state
Drugs[2]	Chronic kidney disease
Amiodarone	Chronic liver disease
Chemotherapies	Hypo/hyper-thyroidism
(e.g., vincristine and cisplatin)	
Colchicine	**Neoplastic**[6]
Hydralazine	Monoclonal gammopathy
Isoniazid	Multiple myeloma
Metronidazole	Primary amyloidosis
Nitrofurantoin	
Nucleosides	**Nutritional**[7]
Phenytoin	Vitamine B12 deficiency
	Vitamine B6 deficiency
Infectious[3]	Copper deficiency
Hepatitis B	
Hepatitis C	**Toxic**[8]
	Alcohol

CMT (Charcot-Marie-Tooth disease); HNPP (Hereditary neuropathy with liability to pressure palsy). (1) Excluded by anamnesis and ad hoc blood tests, (2) excluded by appropriated anamnesis and medical record study, (3) excluded by ad hoc serologies, (4) excluded by negative familial anamnesis and neurophysiological findings, (5) excluded by ad hoc blood tests, (6) excluded by ad hoc blood tests, clinical and neurophysiological findings, (7) excluded by blood test and nutritional status assessment, (8) excluded by anamnesis and blood tests.

We have summarized all demographic and clinical data as well as main ancillary test results in Table 2. Main electroneuromyography (ENMG) data related to the demonstration of a polyneuropathy in our patients are summarized in Table 3.

2.1. Patient 1

Patient 1 developed muscle weakness, exercise intolerance and fatigue at age of 9 year. During adulthood he progressively complained of dyspnea, dysphagia and fecal incontinence. Clinical neurological examination showed a proximal and axial muscle weakness as well as join contractures. A few years later at age of 39 years, he complained of hypoesthesia and balance impairment. Neurological examination showed total absence of tendon reflexes on the lower limbs and pes cavus. Romberg sign was also present.

ENMG, initially consistent with a myogenic disease, later confirmed a sensory polyneuropathy on the lower limbs.

The CK level was measured at the level tenfold upper normal value (UNV). GAA enzyme activity measurement showed a diminished activity [< 1 nmol/mg/h (normal values: 20.4–49.8)] suggesting a LOPD. An extensive blood work-up related to polyneuropathy etiology research was unremarkable. *GAA* gene analysis detected two pathogenic mutations (c.−32–13T>G; c.2608C>T). The patient started a recombinant human acid alpha-glucosidase (rhGAA) enzyme replacement therapy (ERT) at the age of 32 years.

2.2. Patient 2

At age of 29 years patient 2 started to complain of muscle weakness and exercise intolerance. Later on he had recurrent falls and dyspnea. Physical examination revealed mild proximal muscular weakness. LOPD diagnosis was made after a muscle biopsy showing myopathic changes with glycogen deposition observed in electron microscopy and low GAA enzyme activity measured in the muscle (27%: 0.017 U/g; normal value: 0.065+/−0.030). GAA gene analysis showed two pathogenic mutations (c.−32–13T>G; c.525delT). The patient had his first rhGAA infusion at age of 42.

Afterwards, at age of 48 he developed a postural instability. Physical examination revealed an areflexia of the lower limbs and reduced distal vibratory sense. ENMG confirmed a lower limb sensory polyneuropathy as well as myopathic changes at the needle examination.

2.3. Patient 3

Patient 3 started to develop muscle weakness and pain at age of 27 years. The weakness was in the beginning prominent to the right scapula then after it was also present in lower limbs. Later, he developed fecal and urine incontinence. At the age of 35 he mentioned a progressive gait unsteadiness. Clinical examination showed lower limbs muscle weakness and hyporeflexia, a positive Romberg's sign and a length-dependent lower limb multimodal sensory impairment. ENMG demonstrated, in addition to myopathic changes, an axonal sensory and motor polyneuropathy.

Ancillary tests conducted to LOPD diagnosis: elevated CK level (2–3 fold upper normal value), myopathic changes including periodic acid-Schiff (PAS) positive vacuoles in the muscle biopsy; and *GAA* gene analysis showed the following pathogenic mutations: c.−32–13T>G, c.258dupC that segregated on both alleles (confirmed by patient's parents study). rhGAA ERT was started at the age of 50.

2.4. Patient 4

Patient 4 presented at the age of 36 fatigue and diurnal drowsiness. These symptoms leaded to perform a polysomnography that had demonstrated a very severe obstructive sleep apnea syndrome. Pulmonary function test showed a forced vital capacity at 46% of the predicted value and was consistent with a restrictive syndrome.

Clinical examination demonstrated a mild lower limbs proximal muscle weakness and a four limbs distal hyporeflexia. Blood analyses showed an increased CK level (two fold upper normal values).

ENMG demonstrated a mild lower limbs sensory neuropathy and some myogenic potential in proximal muscles.

Table 2
Demographic and clinical data of LOPD patients with polyneuropathy.

Patient, gender, age (years)	P1, Male, 45	P2, Male, 52	P3, Male,57	P4, Male, 39
LOPD-related data				
Demographic data				
Age of first symptoms (years)	9	29	27	36
Age of diagnosis (years)	9	42	50	37
Age of the first rhGAA infusion (years)	32	42	50	37 (clinical trial)
Symptoms				
Muscle weakness	+	+	+	–
Exercise intolerance	+	+	+	–
Muscle pain	–	–	+	–
Dyspnea	+	+	–	–
Other	Fecal incontinence, fatigue, dysphagia	Recurrent falls	Right scapular weakness, fecal and urine incontinence, dysphagia	Fatigue, diurnal drowsiness
Clinical Examination				
Proximal and/or axial muscle weakness	+	+	+	+
Join contractures	+	–	+	–
Other				
Restrictive syndrome	+	+	+	+
Nocturnal non invasive ventilation required	+	+	–	+
Heart involvement	–	–	–	–
Ancillary tests results				
Increased CK level (x UNV, maximum)	+ (10)	+ (1–2)	+ (2–3)	+ (1–2)
ENMG results	Myogenic	Myogenic	Myogenic	Myogenic
Muscle biopsy results	n.a.	Aspecific myopathic changes; glycogen deposition on electron microscopy	Vacuolar myopathy (PAS positive vacuols)	Aspecific myopathic changes; positive intracytoplasmic acid phosphatase staining
GAA enzyme residual activity assay				
Blood (DBS)	n.a.	n.a.	n.a.	< 0.02 μmol/L/h (0.97–8.77)
Fibroblasts	< 1 nmol/mg/h (20.4–49.8)	n.a.	n.a.	5.1 nmol/mg/h (18.6–56.7)
Other tissues	n.a.	muscle: 27% = 0.017 U/g (0.065+/−0.030)	n.a.	None
GAA gene analysis results (HGVS nomenclature)	c.–32–13T>*G*; c.2608C>*T*	c.–32–13T>*G*; c.525delT	c.–32–13T>*G*, c.258dupC[2]	c.–32–13T>*G*, c.1115A>T
Concerning the second mutation*				
Exon	18	2	2	7
Change at the protein level	p.Arg870*	p.Glu176Argfs*45	p.Asn87fs*9	p.His372Leu
Effect	Very severe	Very severe	Very severe	Potentially less severe
Polyneuropathy-related data				
Demographic data				
Type	Sensory neuropathy	Sensory neuropathy	Sensory-motor neuropathy	Sensory neuropathy
Age of first symptoms (years)	39	48	35	No symptoms
Age of diagnosis (years)	39	52	40	37
Symptoms				
Neuropathic pain	–	–	–	–
Balance impairment	+	+	+	–
Hypoesthesia	+ (hand's fingers)	–	–	–
Clinical Examination				
Pes cavus	+	–	–	–
Distal amyotrophy	–	–	+	–
Romberg's sign	+	n.a.[1]	+	–
Hypo/areflexia	+	+	+	+
Distal paresis	–	–	–	–

(*continued on next page*)

Table 2 (*continued*)

Patient, gender, age (years)	P1, Male, 45	P2, Male, 52	P3, Male,57	P4, Male, 39
Length-dependent sensory impairment				
Tact	–	+	+	–
Pinprick	–	+	n.a.	–
Pallesthesia	–	+	+	–
Kinesthesia	–	–	n.a.	n.a.
Ancillary tests results				
Polyneuropathy-related blood work-up	Unremarkable	Unremarkable[3]	Unremarkable	Unremarkable
ENMG results	Lower limbs sensory polyneuropathy	Lower limbs sensory polyneuropathy	Lower limbs sensorymotor axonal polyneuropathy	Lower limbs sensory polyneuropathy

LOPD: late-onset Pompe disease, rhGAA: recombinant human acid alpha-glucosidase enzyme therapy, CK: creatine kinase, UNV: upper normal value, ENMG: electroneuromyography, GAA: acid alpha-1,4-glucosidase, DBS: dried blood spot, HGVS: Human Genome Variation Society, n.a.: not available, PAS: periodic acid-Schiff. (1) Very severe unseadness with open eyes. (2) Fitting segregation for compound heterozygous. (3) A B12 vitamin deficiency was demonstrated five years after the occurrence of balance impairment, previous available vitamin B12 assays being normal.

Table 3
Electrophysiological data.

	P1 Sensory neuropathy	P2 Sensory neuropathy	P3 Sensory-motor neuropathy	P4 Sensory neuropathy	Normal values
Age at the time of electrophysiologic examination	39	52	54	37	
Motor nerve conduction study					
Right peroneal nerve					
Distal latency (ms) [%]	3.6	4.2	**NR**	3.3	≤ 5.5 ms
Ankle (distal) CMAP Amplitude (mV) [%]	**2.5**	5.9		**1.8**	≥ 2.8 mV
Fibular head CMAP Amplitude (mV)	2.3	5.9		1.4	
Knee CMAP Amplitude (mV)	2.3	5.8		n.a.	
Ankle-fibular head segment Velocity (m/s)	49.7	43.0		42.1	≥ 40 m/s
Fibular head-knee Velocity (m/s)	51.3	47.0		n.a.	≥ 40 m/s
F-wave latency (s)	47.1	**57.9**		n.a.	≤ 56 ms
Conduction block	no	no		no	
Temporal dispersion	no	no		no	
Sensory nerve conduction study					
Right sural nerve					
Latency (ms)	**3.2**	**3.9**	**3.7**	2.7	≤ 3.1
SNAP amplitude (μV)	**2.1**	**3.4**	**1.6**	**5.8**	≥ 6
Velocity (m/s)	40.8	**35 (temp.: 29 °C)**[1]	**33.6 (temp.: 30.4 °C)**[2]	**36.4**	≥ 44
Left sural nerve					
Latency (ms)	**3.2**	**4.2**	**NR**	**3.4**	≤ 3.1
SNAP amplitude (μV)	**2.2**	**5.3**		**1.9**	≥ 6
Velocity (m/s)	43.7	**33 (temp.: 29 °C)**[3]		**35.2**	≥ 44

CMAP: compound muscle action potential, SNAP: sensory nerve action potential, NR: no response, n.a.: not available. Underlined bold values are out of the normal range. (1) Corrected velocity value using de Jesus formula [6] was 38.0 m/s, below the normal range. (2) Corrected velocity value using de Jesus formula [6] was 34.4 m/s, below the normal range. (3) Corrected velocity value using de Jesus formula [6] was 35.9 m/s, below the normal range.

The muscle biopsy revealed nonspecific myopathic changes with a positive intracytoplasmatic acid phosphatase staining. GAA enzyme activity was very low in the blood [< 0.02 μmol/L/h (0.97–8.77)] and fibroblasts [5.1 nmol/mg/h (18.6–56.7)]. GAA gene analysis revealed the following pathogenic mutations: c.−32–13T>G, c.1115A>T. ERT was started at the age of 37.

3. Discussion

Among our six LOPD patients, two third ($n=4$) had a polyneuropathy of undetermined etiology.

Pompe disease is a multi-systemic disease involving glycogen deposition in many tissues [1]. Its pathophysiological basis linked to glycogen deposition in peripheral nerves may be postulated as an additional morbid condition in LOPD.

Nerve conduction studies in myopathy are generally normal, except if distal muscles are affected. In that case the compound muscle action potential (CMAP) amplitudes tend to be reduced while the distal latencies and conduction velocities are preserved. It reflects the muscle damage in the face of normal nerve function. Sensory nerve conduction studies are expected to be normal

in myopathies, unless there is a coexistent neuropathy [7].

Currently LOPD disease modifying therapy is based on the replacement of the reduced GAA enzyme. Starting as early as possible ERT is justified when patients are symptomatic or develop an organ involvement due to the disease that can be demonstrated by ancillary tests [3]. The number of LOPD asymptomatic patients is thought to be increasing due to the development of numerous programs of Pompe disease screening. rhGAA ERT is usually well tolerated, but occasionally allergic reactions may occur. ERT-induced polyneuropathy has never been described after more than ten years of ERT use, including more than thousand patients treated all over the world. In addition, to the best of our knowledge no biological proof-of-concept concerning potential ERT-related peripheral nerve toxicity is reported in the literature. Finally, half of our patients (P3 and P4) were diagnosed as having a polyneuropathy before starting ERT.

The possibility of a casual association between an idiopathic neuropathy and LOPD also seems unlikely since it tends to affect patients in the sixth decade or older [8] and the first symptoms of polyneuropathy were observed in our patients between the age of 35 and the age of 48.

Concerning the patient 1, despite the presence of a pes cavus conformation, we assumed that an inherited polyneuropathy was unlikely since the neuropathy was clearly axonal and the most prevalent Charcot-Marie-Tooth (CMT) polyneuropathies are demyelinating in Western Europe. Moreover, the family history was negative and no consanguinity was known on the patient 'parents. That made the probability of co-occurrence of two rare diseases very unlikely.

For patient 3, we must notify that a B12 vitamin deficiency was demonstrated five years after the occurrence of balance impairment. However, as previous available vitamin B12 assays were normal, it makes unlikely that was the cause of the neuropathy.

We need to underline that our study concerns a small cohort of patient and that prevalence data may not be extrapolated from our observation. Moreover our observation certainly needs to be confirmed on large samples.

Both LOPD patients and their physicians may easily overlook a potential polyneuropathy because postural imbalance or difficulty walking could also be explained by the progression of the myopathy. Polyneuropathy diagnosis in LOPD patients has potential important consequences in the patient's management since this condition could increase patient disability, especially due to proprioception and balance dysfunction as well as a potential peripheral autonomic system involvement.

4. Conclusion

Despite we cannot definitely exclude a casual association in the patients we have described, our observation supports that polyneuropathy could be an additional comorbid condition in LOPD patients.

Screening of polyneuropathy should be performed in LOPD patients in order to avoid missing this potentially disabling condition that carries a specific management pathway including avoidance of neurotoxic drugs, proprioceptive physiotherapy or neuropathic pain targeted painkillers drugs.

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